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OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

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MEMORANDUM

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SUBJECT: Ethylene Thiourea. Joint Review by EPA and PMRA of Protocol for Extended One-Generation Reproductive Toxicity Study

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The US EPA Office of Pesticide Program and Health Canada's Pest Management Regulatory Agency (PMRA) held a teleconference on January 6, 2011 to discuss a preliminary protocol for an extended 1-generation reproductive toxicity study with ethylene thiourea submitted by the Dow Chemical Company.

This memo addresses issues discussed during that teleconference and in subsequent emails. The EPA and PMRA jointly agree that the following revisions to the draft protocol are needed to satisfy the data requirements for ethylene thiourea.

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The protocol should follow the latest version of the OECD guidelines for an extended 1-generation reproductive toxicity study. The document can be found at this web site: http://www.oecd.org/dataoecd/23/10/46466062.pdf.

The estrous cycle should be evaluated in parallel with an evaluation of corpora lutea (page 15, estrous cycle evaluation).

The list of triggers for producing a second generation (table 3 on page 17) should also include offspring endpoints per the OECD guidance.

The F1 offspring should have primary follicle and small growing follicles evaluated in parallel with the estrous cycle evaluation (page 34).

A tiered approach for ovarian follicle enumeration as outlined below is recommended. This is important because, when the second generation is not assessed, the enumeration of ovarian follicles and corpora lutea are the only measure of fertility in females that were exposed in utero.

1. Conduct a quantitative evaluation of the F1a primordial and growing follicles in at least 1% of the ovary as a screening measure for potential adverse effects. If the results are within 10% of controls, no further action is required. If results are less than 90% of controls, the following is required:
2. Conduct a quantitative evaluation of the F1a primordial and growing follicles in at least 5% of the ovary as a definitive measure for potential adverse effects. If results are equivocal, the following is recommended:
3. Conduct a quantitative evaluation of the F1b primordial and growing follicles in at least 5% of the ovary as a definitive measure for potential adverse effects.

Immunotoxicity testing is not a part of the protocol. Both US EPA and PMRA recommend that a developmental immunotoxicity cohort be included in the extended 1-generation study, as per the November 2010 OECD guidelines referenced above. If this cohort is added in accordance with the OECD guideline, it is expected to address both juvenile and adult immunotoxic effects and to satisfy the US EPA requirements (40 CFR Part 158) for immunotoxicity testing in adults.

Because of problems with stability of test material in feed in several of the previously submitted ETU studies, the stability of ETU in feed should be assessed before beginning the extended 1-generation study.

The protocol states that perfused brains from low- and mid-dose animals will be held for possible morphometric examination. The tissues should be preserved in a manner such that deterioration of tissues will not prevent future subsequent examination.

Positive control data for the neurotoxicity examinations should be included or cited in the final report.